

5-1-1932

Hyperthyroidism in pregnancy

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SENIOR THESIS

"HYPERTHYROIDISM IN PREGNANCY"

J.R. COOPER.

INTRODUCTION

The main object of this paper is merely to review the important work done in the past few years on the relationship of the thyroid gland, and its abnormalities, to pregnancy. While the literature considered in this monograph is limited almost entirely to the majority of the research since 1926, reference will be made from time to time to the work of an earlier date. Thus, this paper becomes an abstract of the work mentioned above, although a few cases from personal experience will be cited at the conclusion but, as the records on these are rather incomplete, they cannot be used as important contributions to this work.

As we must necessarily limit ourselves at some point in a paper of this sort, the anatomy, histology, and organology of the normal thyroid will not be considered, although brief mention will be made of the physiology of the normal and the pathology of the abnormal gland.

It is also practically impossible to consider hyperthyroidism or hyperfunction of the gland, without giving some thought to the reverse condition, if only out of fairness to the authors who have contributed so much to the latter. Therefore, this work will be briefly reviewed.

As the relationship of the thyroid to the other glands

of the endocrine system is a subject within itself, this relationship will also be only briefly considered, although it is an important consideration and warrants farther work.

The history of the studies in regard to the main topic will also be alluded to briefly, but the main text of the work will concern itself only with the relationship of hyperthyroidism and hypothyroidism to pregnancy and the effect of pregnancy upon those two conditions. To this will be added the effect of thyroid abnormalities that cannot be classed as hyperthyroidism and their effect upon pregnancy and the effect of pregnancy upon them.. The treatment of the above conditions will be considered as thoroughly as possible.

At the present time it is well recognized that the bodily functions are not controlled entirely by nerves and their influences but also by chemical substances passing from the tissues into the blood stream. Substances derived from one organ may influence other substances from another organ after passage into the blood stream and these have been called chemical messengers or hormones by Starling.

While it was fairly simple to study the glands which were found to have ducts, it was not so easy to find the function of the ductless glands as the thyroid, parathyroid, thymus, hypophysis, and epiphysis and the adrenals. Brown-Sequard receives the credit for impressing the medical world with the view that all glandular organs, whether they have ducts or not, gave to the blood certain substances that were necessary to the welfare of the body. The essential

correctness of his conception is now fairly well

recognized and the endocrine system at the present time includes in addition to the glands listed above, the liver the pancreas, the duodenal mucosa, and the sex glands.

Demonstrations of the incertions of these glands have been proved by the excission of the gland and the resulting effect on the bodily activity. Then the study of the effect of injection of glandular extracts upon the body, following the excission.

In the case of the thyroid, as with the other glands of internal secretion, there are two types of disturbances, namely hyperfunction and hypofunction. Knowledge of the function of the thyroid is more comprehensive than that of the other glands, and it is regarded as a regulator of bodily metabolism. The active principle, thyroxin, is said to be carried to every cell of the body by the blood and after abolition of the thyroid the activity of all cells is reduced to about forty percent below normal and the total activity of the animal becomes almost reduced to that of a vegetative organism. This is the cause of the clinical symptoms in the condition known as hypothyroidism and was first recognized in 1873 by Sir William Gull, myxedema being described five years later by Ord.

The opposite condition or hyperthyroidism, is produced by the administration of excessive amounts of thyroid preparations or by the abnormal stimulation of the gland. This condition also causes a definite clinical syndrome and these symptoms will be taken up later in connection with the work of the various investigators. (18)

One of the earlier works on the problem of hyperthy-

oidism in pregnancy was Gellhorn(13) who, in 1913, reported his findings in a case report in which he found it necessary to remove a fetus from a mother who was about twenty-two weeks pregnant. He stated that when the symptoms of Graves disease were aggravated, even with conservative and medical treatment, interruption of the pregnancy was indicated without delay and that the quickest, and therefore the best method of interruption was by vaginal Caesarian, under spinal anesthetics. It was Gellhorn who set forth the hypothesis that if Grave's disease is well developed in girls they should not marry, if the disease had appeared since marriage conception should be prevented, and if they become pregnant vaginal Caesarian with tubal sterilization should be done. He held that even though the symptoms were slight, grave danger to the mother might result.

The work of Gellhorn had been cited with a definite object in mind. Goiter had been observed and studied early by the Chinese, Greeks, and Romans, and the latter were the first to notice thyroid hypertrophy in connection with pregnancy.(10) (32). Parocelsus made notes on the relations of simple goiter and myxedema and through all the following centuries a feeling existed that iodine played a part in the various thyropathies as is evidenced by the remedies of iodine-containing substances. There was apprehension but no comprehension of what is now so clear, as it was only a little over thirty years ago that Bauman of Freiburg demonstrated iodine in organic combination with thyroid tissue. However, it was not until 1914 that Kendall isolated thyroxin (32) and this is after the work of Gellhorn

and ideas of treatment have changed considerably since 1913.

Robertson(32) admirably reviewed the keynote of thyroid pathology as expressed by Marine, which is that when the iodine content of the gland is decreased below .1% per gram of the dried gland tissue, definite morphologic changes take place in the form of a cycle. The gland first passes from normal to hypertrophy then to hyperplasia. From this point it may become atrophic through exhaustion or recover and pass into the colloid or resting stage, but never returns to normal. From this colloidal stage the cycle may be repeated several times. Therefore, the main thought in treatment is, "How can the balance of iodine metabolism be best maintained, or if badly deranged, how restored?"

Many factors share in the disturbance of the normal storage quota of iodine in the thyroid, chief of which is "iodine starvation". It is well known that our iodine supply comes largely thru the water supply and in goiterous districts the water contains little or no iodine and this substance must be supplied as will be demonstrated later. The factors in iodine dissipation are largely the unusual demands made on the thyroid to furnish more thyroxin to the tissues than the reserve storage can safely do, and in this stage of more activity in all walds of life there is small wonder that unusual metabolism is necessary to maintain the strain and with a relative expenditure of iodine. Excesses in use of fats and proteins increase the loss of iodine by increasing the metabolic rate. Interference in iodine absorption and utilization through the effects of focal infections, intestinal flora, and various toxins plays a large part in goiter problem,

and it is in this condition that the work of McCanison fits into the picture. He showed that endemic goiter could be induced and reduced at will by contamination of food and water supply. These results have also been obtained by Harding(16), who dwells more on the products excreted and withheld in the body.

There are several classifications of abnormal thyroids or "goiter" and these will be considered as the various author works are reviewed. Robertson considers two forms of **non-toxic** goiter, the colloid and the adenomatous, and these are easily identified. The ruling out of other pathology causing the symptoms must be done. Is the rapid pulse a neurotic phenomenon, a true organic heart lesion, or a tuberculous phenomenon? Is it the result of pelvic pathology, a psychoneurosis, or a vagatonia? No matter how closely the symptoms resemble hyperthyroidism, this must be proven by examination. Incomplete preliminary study is a great source of **error**. The non-toxic goiter does not require treatment until pressure symptoms are present. The colloid type usually ~~d~~isappears in the early twenties regardless of treatment, but it may be reduced by thyroxin or iodine.

The adenoma may remain quiescent from the cradle to the grave but it holds important potentialities. Virtually all carcinomata of the gland originate from this condition. They are susceptible to activation by the use of iodine and may become toxic from this drug. They are not responsive to medical treatment and should be left alone or referred to the surgeon and the patient told of the possibilities.

In this classification the term hyperthyroidism includes

Grave's disease and toxic adenoma. They present the clinical syndrome of tachycardia, loss of weight, the marked nervousness etc., but this needs verification. The basal metabolic rate is to hyperthyroidism what the Kahn and Wassermann are to syphilis, and it is the logical chemical reaction that must result from thyroid activity; from the dormant gland of the cretin to the violent activity of Grave's disease. (32) It is the one test which classifies thyroids into the hyper and hypo-groups. Hyperthyroidism does not exist without increased metabolism. A clear cut case of toxic goiter is a surgical problem and iodine should be used only as a surgical accessory and not as a remedial agent, and this medication should be controlled by the surgeon. The diet should be forced to the limit of digestion, high in fats and carbohydrates but low in protein and rest in bed, luminal or bromides with digitalis should be used if necessary.

In hypothyroid conditions are included the cretin, whose thyroid is starved before birth and the myxedema whose thyroid exhausted itself after birth. Then there may be the borderline cases without edema, but who are overweight, sleepy, tired mentally and physically, lazy, with low temperature, slow pulse and low basal metabolic rate. All these require thyroid extract and respond to it. In the administration of thyroid to adults and to children we must expect practically opposite results, as in children there is an anabolic metabolism and in adult a catabolic one.

Topper and Cohen (1928) found the effect of thyroid on normal children to be nil as far as pulse rate, nervous phenomena and basal metabolic rate were concerned, but a remark-

able effect on their growth was noted. In the cases where hypothyroidism was evident the use in pulse rate, temperature and basal metabolic are was constant. In the prescribing of thyroid it is well to remember Kendall's words, "It will increase the the phase of metabolism that is dominant in the individual". Hyperthyroidism is exceedingly rare in children but hypothyroidism is common. This is because a large percentage of thyroid disorders arise in utero as the fetus is starved of its normal iodine supply by the mother. Robertson favors the administration of iodine to all pregnant women in goiterous areas, providing they are not harboring adenomata.

The treatment of goiter, then, as understood today, must be one of prophylaxis. The thyropathies are preventable disease just as much as small-pox, malaria, etc. We should live in the hope that someday the mutilation of thyroidectomy will be a thing of the past and presence of goiter in a community will be a reflection on the sanitary conditions.

With these words of introduction regarding abnormalities of the thyroid we had best turn to the effect of these conditions on pregnancy.

The number of women affected by hypertrophy of the thyroid gland during pregnancy is conservatively estimated at 40% by Hinton (20), while some writers place it at 90%. The number varies with the district from which the statistics were taken, i.e. goiter belt or sea coast and the etiological factors concerned have been discussed. Some refer to this hypertrophy as a physiological enlargement, but the evidence at present would indicate it to be a diseased thyroid state

or pathologic enlargement. Hinton refers to the primary enlargement and not to the pre-existing enlargement that is aggravated by pregnancy. That excessive demands are made on the thyroid at the time of pregnancy is born out by the enlargement in multiparae at the fifth month and in primiparae not until the sixth month. Three types or stages of goiter are recognized, including colloid, adenomatous and exophthalmic. Whether these represent separate diseases or stages of the same disease or a continuous process is still unsettled, but Hertzler believes that the different types of goiter represent stages in a continuous process and this view is also born out by Rienhoff and Helling(31)and(17). The latter does not agree with the findings of Rienhoff in the pathology of the abnormal thyroid of Grave's disease. Thirty of these goiters taken from treated patients at autopsy were compared with thirty untreated glands and there were no changes in vascularity or amount of fibrous tissue found. The acini were not round, smooth-walled, or regular size and form. No small tumefactions or colloid cysts were visible with the naked eye. In 84% the only difference was in the colloid and here they found more stained colloid after treatment. This, liquefaction of the colloid seems to be the chief characteristic of exophthalmic goiter. (17)

Hinton, after studying sections of the thyroid gland in stillborn infants and in persons to eighty nine years of age who met with accidental death was forced to conclude that a correct diagnosis of thyroid disease cannot be made from either the clinical picture or histologic sections alone, but that both must be studied. (20)

Wayne Yoakam f(40) found that out of 937 consecutive cases in obstetrics, of which there were about an equal number of primiparae and multiparae, that the incidence of thyroid enlargement was sixty percent. Levin (23) in 1921 working in the goiter belt of Michigan, found this percentage to be 73% in a series of 1783 patients. In Yoakam's series 20% had lived in the goiter belt for one to three years.

Gardner-Hill (12) called attention to Tait's observation in 1875, of the step-like enlargement of the simple goiter in successive multiple pregnancies and also showed that this obtained in the majority of 26 cases of simple goiter under his observation. Von Graff noted marked increase in simple goiter in 38.5% of pregnant women coming under his observation. Dock and Lisses called attention to the increase in size during pregnancy and the rapid decrease after confinement.

Falls (9) states that control of the function of reproduction is entirely under the control of the vegetative nervous system. This control is governed in part by the action of certain hormones or secretion's of the ductless glands. Thus, deviations in the ductless glands of the pregnant from the normal nonpregnant state may be found. The anterior lobe of the hypophysis may be greatly enlarged (Meyer Falta) and there is also evidence that the thymus, epiphysis, parathyroids, and Langerhans Islands of the pancreas are also functionally altered. The thyroid is one of the most notably altered and the enlargement may be appreciated clinically in many cases, and in some there appears first during pregnancy a true adenomatous growth with symptoms of toxic adenoma.

No one man has had more experience in this type of obstretical complication. (9)

The most valuable work of a recent date dealing with the relationships of the ovary and gestation to the thyroid disease is probably that of N.M. Knude, et al. (22). These workers felt that the evidence and clinical observations in hyperthyroidism and pregnancy are inadequate and that the number of cases studied is too few. This work is not the first of its kind as Guddenatch (1915) fed fresh thyroids to rats until emaciation, diarrhea, muscular weakness, and in some instances death occurred and the above signs were accompanied by changes in the coat, as "The hair becomes yellow, strands on end, sometimes falls out in patches, and the entire coat looks ragged." Mating in these animals usually brought no results, pregnancy was delayed since fertilization did not occur until several weeks after the thyroid was discontinued. Pregnancy when it did occur resulted either in abortion of the young or the young died soon after birth. In late pregnancy the young showed diminished tendency to grow, and, although not fragile, their size was smaller than the normal offspring.

Hoskins (1910) subjected pregnant Guinea pigs to thyroid feedings with intent of influencing the gland weight in the offspring. The results were variable as follows: One died of hyperthyroidism after eight days of feeding 0.1 gram per day, whereas another survived for the same period on a dose twenty-five times as great. Abortions were frequent in the surviving animals.

In the studies of Knude it was found that the ovaries of

cretin rabbits presented a histological picture which differs in many respects from the normal. Hofmeister (1893-94) found that in rabbits eight months old and thyroidectomized at four and one half months after birth, that cross-sections of their ovaries showed very large follicles closely packed together. He described premature ripening of the follicles and a condition which Zligler called "follikulare hypertrophe". These rabbits were more than half grown when thyroidectomized but even so the disturbance in ovarian development was marked. This has been noted by other investigators.

Cretin rabbits were produced by removing the thyroid about three weeks after birth and allowing the animals to remain in cretin condition for several months. (It was noted that pronounced cretins most frequently resulted if the thyroids were removed before the animals were three weeks old; complete thyroidectomy within two weeks after birth usually resulted in death from parathyroid tetany even though the lower pair of parathyroids remained. This interesting in as much as the same operation performed one week later is not followed by symptoms of parathyroid deficiency) Desiccated thyroid was fed in varying amounts (60 mgs to 14 mgms) per day over a period of four to eight weeks, or until symptoms of severe hyperthyroidism were present. Histological sections of the ovaries then revealed large numbers of primary follicles and apparently normal Graafian follicles in all stages of development. The significance of these observations becomes more important when associated with our present knowledge of the development of the primordial ovum.

The accepted theory relative to the development of the

egg cell holds that these cells are present in the ovary in their final numbers at birth. Minot states that at all ages small egg cells together with their follicles present a constant appearance and remain for a long time without change, but, from time to time, certain ones develop. In a pronounced cretin, thyroidectomy performed at three weeks, and allowed to reach maturity in a marked hypothyroid condition, only a few follicles are seen near the surface of the ovary, but, in a cretin rendered hyperthyroid, great numbers of the primary follicles are easily seen. These essential facts seem contradictory to the theory that all the cells are preformed at birth. Granting in that event that the cretinism caused their degeneration, no postnatal influence, as hyperthyroidism could possibly call forth their subsequent appearance.

Whether the ovarian atrophy is specifically due to the thyroid deficiency, or to the more general physiological disturbance, secondary to the hypothyroidism has not been determined. The marked anemia constantly accompanying cretinism in the rabbit should be considered, but cannot be the essential factor in as much as clinical cases of pregnancy have been reported in women with an equal degree of anemia.

Despite the evidence of apparently active ovaries in cretin rabbits fed for a long period with large amounts of thyroid, and the evidence of mating, these animals rarely, if ever, gave birth to young. In order to throw light on the mechanism of this phenomenon, the following experiments were performed: Eighteen female rabbits were fed desiccated thyroid in doses varying from 90 to 660 mgms. per rabbit per day. Varying amounts were used because of the variations

in susceptibility to the thyroid substance in the different rabbits. In some of the animals severe hyperthyroidism was induced before mating. Others were normal at the time of mating, but in these the thyroid feeding started on the same day as mating. The evidence for effective mating was obtained, first by finding the sperm in the vaginal smears of isolated females which had been placed in the mating cage for not more than one hour. Second, by palpation of the fetuses about eight days after observing sperm in the vaginal smears. Third, by performing laparotomy and counting the fetuses on the seventh to the fifteenth day of gestation.

The data showed that in the nine rabbits with laparotomy the fetuses counted on the seventh to the fifteenth day of gestation varied in number from nine to fourteen. Only two living young were born of this group, i.e. two animals gave birth to one living young. One gave birth to one well developed dead fetus at term and one delivered one immature dead fetus before term. Two delivered two dead. Two rabbits died during the last week of gestation and autopsy revealed almost complete resorption of the fetus.

Laparotomies were not performed on the second group, thus ruling out the possibility of the surgical intervention interfering with the development of the fetuses. One rabbit in this group gave birth to two living young and three dead young at term. In all the others the fetuses were either completely resorbed or one to three dead rabbits were delivered. The results of these experiments show that there is an apparent increase in the number of developing Graafian follicles and

and primordial ova may be demonstrated in the ovaries of cretin rabbits converted into a condition of severe hyperthyroidism by the injection of thyroid substances. Also, in rabbits with severe hyperthyroidism, experimentally produced, the process of oestrus, ovulation, fertilization, migration, and implantation takes place, but, in most instances the young are never born, resorption occurring instead during the latter two-thirds of pregnancy.(22)

Schlotthauer and Caylor (34) working with pregnant swine found that thyroidectomy does not effect these animals if they receive two grains each of dessicated thyroid extract for sixty days or more following the operation. The symptoms of thyroid deficiency in pregnant sows were influenced by the diet of the animals. Thyroidectomized animals on a balanced diet revealed signs of myxedema, whereas those on a high carbohydrate, low protein diet did not develop the edema of myxedema and were under weight (allowance being made for the pregnancy). The offspring of these swine did not differ from those of the control animals except that there was a variation in the weights of the thyroid glands.

There is not much controversy regarding the symptoms of hyperthyroidism as these are fairly well standardized. These are nervousness, tachycardia, tremor, loss of weight, sweating, enlargement of the gland, occasionally nausea and vomiting, but most important of all an increase in the basal metabolic rate. Clinical manifestations vary with the patient and also with the stability of the thyroid function in the non-pregnant state. The patients who present themselves for study in this connection may have, before becoming pregnant, hyperthyroidism; normal thyroid function or hypothyroidism.

The woman with a normal thyroid function, on becoming pregnant, usually will give evidence of a mild hyperthyroidism, if the signs are carefully looked for. Thus, nervousness, tremor, nausea, and vomiting, weight loss, sweating, enlargement of the gland and sometimes slight exophthalmia may be noted in the pregnant woman with normal thyroid function, and this not infrequently. Many of these signs and symptoms have been pointed out for years by obstetricians as signs of pregnancy without attempt to explain their fundamental significance. It is said by Falls (10) that women with pronounced hyperthyroidism will developed, rarely become pregnant. Even so, it is widely recognized at present that a basal metabolic rate is absolutely necessary in the correct diagnosis of hyperthyroidism.

When pregnancy does occur in pronounced hyperthyroids a curious reaction may occur. In one group of the symptoms are greatly aggravated and this may be so extreme that radical measures may be necessary. On the other hand, the symptoms may become greatly ameliorated and continue so until the termination of the pregnancy when the symptoms will recur. In some cases there is only mild stimulation of the toxic symptoms.

It is not easy to explain what happens, but it is believed that during pregnancy there is a stimulation of the sympathetic nervous system and all the glands of secretion. As a result of this there is a readjustment of these glands relationship to each other and to the organism as a whole. When this takes place in the right direction they are aggravated. With this conception it is hard to agree with the dictum of Gellhorn (13).

There is a group of women who have pregnancy complicated by

toxic adenomata. The basal rate and thyrotoxic symptoms are less marked in these, as a rule. There may be, however, serious symptoms due to pressure on the trachea and interference with respiration. Massey (25) warns especially in these cases against the indiscriminant use of iodine in the form of Lugol's solution. Falls (10) does not exactly agree with this conception, as we shall see later.

Finally, there is a group who present themselves with the picture of hyperemesis gravidarum, and in whom the clinical evidence of thyrotoxicosis is completely masked by the hyperemesis. The more these are studied, the more Falls(10) is convinced that there may be a thyrotoxic element in most cases hyperemesis.

Therefore, the pregnant state may be complicated by mild hyperthyroidism, exophthalmic goiter and toxic adenoma, and these patients may be regarded as having a physiologic reaction and no treatment advised. Also, patients with hyperemesis gravidarum should be carefully examined for evidence of hyperthyroidism.

How, then, is it possible to determine whether the symptoms are due to hyperthyroidism or to a nearly normal reaction to the pregnancy? Basal metabolic tests must be made frequently to rule out a pathological thyroid. It is generally agreed that there is an enlargement of the thyroid gland in approximately 60% of pregnant women(40), and there is also an increase in the basal metabolic rate in pregnancy. (28) This, however, is due to the increasing mass of active protoplasmic tissue, consisting of a large part of the fetal tissues, and in lesser part of maternal structures, and is very moderate in extent (37).

This is supported by the fact that subtraction of calculated heat production of the fetus from the total heat produced by the pregnant woman leaves the metabolic rate unaffected by gestation also, almost immediately after delivery the metabolic rate falls to a point corresponding to that of early gestation. In terms of Aub-Dubois standard- the total increase due to the rapid metabolism of fetal tissues rarely amounts to more than 15%. Thus any rate above 20% increase is considered abnormal.

Mussey, Plummer and Boothby (26) say that "a basal metabolic rate of plus 25 or even plus 30 is not necessarily an indication of hyperthyroidism in the latter months of pregnancy," and thus recognize the occasional variation brought out by Gustafson and Benedict that "even among ten presumably healthy persons, one or more will have a metabolism deviating more than plus-minus 10% from the standards." It therefore seems well demonstrated that a high basal metabolic rate, unsupported by clinical evidence of hyperthyroidism does not warrant a diagnosis of abnormal thyroid activity.

In the series of seventy-two cases, studied by Plass and Yoakam (28), the patients were divided into four groups, according to the clinical condition of the thyroid gland. Group I--21 cases-- had normal thyroid glands; group II--23 cases --had small colloid (endemic) goiter; group III--18 cases--had adenomatous goiter; and group IV--10 cases-- had large colloid (visible) goiter.

Clinical differentiation was made at the patients first visit to the clinic, on a basis of careful palpations. Additional observations were made at monthly intervals during pregnancy, and more frequently in the puerperium. All metabolism tests were made by technicians as part of their

routine work. Aub-Dubois standards were used and patients came to the laboratory between eight and ten o'clock in the morning, the last food being taken the evening before. Tests were made at four-week intervals, usually from the fourth lunar month. After delivery, two or three determinations were obtained in the first two weeks and another, if possible, at six weeks. Results of tests which were, for any reason, unsatisfactory were discarded. Private patients only were utilized and full cooperation demanded. Most of the patients were primiparous.

In each group there were numerous patients who had normal metabolic rates which never rose above plus 20. In this group the average increase in basal metabolic rate was from plus 1 in the third lunar month to plus 9 in the tenth lunar month, while in the first week after delivery the rate fell to plus 1 the early pregnancy point. In the late puerperium there was a progressive slight fall to an average of minus 7 in the third week. This curve is consistent with the work of previous workers (Sandiford and Wheeler (37) Rowe, Alcott and Mortition, Root and Root, etc.), and confirms the observation that lactation is not associated with increased metabolism. Diminished physical activity has been held responsible for the observed postpartum fall in the basal metabolic rate.

Other data obtained during the tests helped to form curves for average variations in weight, pulse, and blood pressure also. The general similarity in the curves was striking. The weight shows an increase during pregnancy of thirty seven and a half pounds with a loss at delivery of twenty pounds and an apparent permanent gain to the body of seventeen and a half

pounds. There was a slight increase in the pulse rate as pregnancy advanced with a drop to normal shortly after delivery. The blood pressure tends to be low early but undergoes a rise in the last month and a slow fall in the puerperium.

Twenty-four (33%) of the seventy-two patients studied showed metabolic rates above the chosen standard of 20 % on one or more tests and were subjected to closer study. The distribution of these cases was as follows:

THYROID GLAND	NORMAL B.M.R.	B.M.R. OVER 20	TOTAL.
Normal	16	5 (24%)	21
Small colloid goiter	15	8 (35%)	23
Adenomatous goiter	12	6 (33%)	18
Large colloid goiter	5	5 (50%)	10

Palpable evidence of thyroid hypertrophy is apparently associated with a greater tendency toward increased metabolism, as might well be expected.

Five of the twenty-one patients with normal thyroid glands had rates above plus 20 %, an incidence which is hardly above the average expectancy of increased metabolism. The curve of the normal above is like the usual course but in each case the metabolism is constantly slightly above the average. Two patients showed a definite pregnancy enlargement of the gland and two others complained of increased nervousness and showed tremor, while only one had clinical evidence of thyroid change. In no case did the symptoms demand treatment and such individuals are probably potential hyperthyroids.

The cases of small colloid goiter with increased basal metabolic rate were considered as instances of true endemic enlargement. There were eight of these cases showing a rise in early pregnancy. In one of these there was a twin pre

pregnancy and the extra load was held responsible for the rise. Some cases showed an increase at first, with a post partum decrease lower than the reading of early gestation. Two others did not come down to the early gestation level at all.

Of the six patients who had adenomatous goiter with an increased metabolic rate, all had clinical evidence of hyperthyroidism except one. In general the rise in basal metabolic rate during pregnancy is greater than in normal individuals and the post partum drop is slower and less complete. Only one patient showed a definite increase in the size of the gland during gestation. Three patients had prophylactic iodine and three were not treated. Among those who received sodium iodide there was no evidence of congenital goiter in the new-born, even though the thyroid enlargement was greater and the basal metabolic rate higher than in the other three who were given no iodine and among whom there were two instances of congenital goiter in the new-born.

In the cases of large colloid goiter, one-half of the group showed an increased basal metabolic rate while one-half were unaffected by gestation. This elevation was attributed to hyperactivity of the gland. Two of these patients had no prophylactic iodine and the infants had congenital goiter. These patients all suffered from hyperthyroidism (mild) if the post partum basal metabolic rate is an indication.

These studies indicate that pregnancy tends to place an extra burden on the thyroid gland which the normal gland can assume without difficulty, but which caused disturbances in those individuals whose thyroids are affected at the time gestation begins. The greater the origin pathologic alteration

ion in the gland, the greater the chance that pregnancy will lead to true hyperthyroidism. An unusual increase in the metabolic rate during pregnancy, with an early post-delivery reading above the early pregnancy value and a slow return of the metabolism to normal can best be interpreted as indicating a true pregnancy hyperplasia of the thyroid. (29)

Information concerning a group of pregnant patients who display many evidences of hyperthyroidism without falling into the class of true toxic goiter was sought by Falls, as well as of those with toxic thyroid. Many pregnant women who show some increased nervous instability, have slightly enlarged thyroid and a fine tremor, were, in reality, affected by a mild hyperthyroidism. These signs and symptoms have in the past been regarded as neuroses or simply part of the changes incident to pregnancy without attemptin to determine what these changes were fundamentally based upon.

Falls shows three groups of clinical manifestations of such symptoms, as follows:

GROUP I. The mildest symptoms noted have been increased nervousness, slight weakness, tremor, tachycardia, sweating and a slight increase in basal metabolic rate. These women were not seriously affected by the altered secretion of the gland, but neither could the abnormal symptoms be totally disregarded or called signs of pregnancy.

GROUP II. This group showed symptoms of toxic adenoma and the gland was irregularly enlarged. There may be difficult respiration and phonation, marked prostration and weakness. The gland may feel nodular and the basal metabolic rate may greatly increased. Tremor, tachycardia, and sweating may be

marked and the giving of Lugol's may aggravate the symptoms. GROUP III. This group includes patients with typical exophthalmic goiter symptoms. There is a marked tremor and tachycardia, and the gland is firm but moderately and diffusely enlarged. There may be gastro-intestinal symptoms as nausea vomiting, and diarrhea. There is usually loss of weight and a basal metabolic rate of plus 100 % or more. Occasionally symptoms of exophthalmic goiter appear for the first time during pregnancy, in others a mild hyperthyroidism is aggravated by pregnancy, while in still others the distinct hyperthyroidism is ameliorated by the pregnant state and relapse may follow the termination of pregnancy.

This, a mild hyperthyroidism as judged by the clinical manifestations and the basal metabolic rate is not an uncommon complication of pregnancy and no special treatment is necessary and many of the nervous symptoms seen in pregnancy are probably due to abnormal activity of the gland indirectly by the pregnant state. Exophthalmic goiter symptoms may develop during pregnancy and be wrongly diagnosed as hyperemesis gravidarum.

Davis (5), in 1926, stated that approximately 41% of the last 520 women examined in early pregnancy had a visible hypertrophy of the thyroid gland. Eight of these had returned with typical symptoms of toxic thyroid within fourteen months after pregnancy. Small doses of iodine had been given during pregnancy but none after delivery and no patient returned with hyperthyroidism less than four months after delivery. Overwork, worry, and other forms of nerve strain appear as contribution causes in each case.

The average metabolic rate of nine women with normal

thyroids at term was plus 2.4% and their average after delivery was minus 1.3%. The average rate of seven women with simple hypertrophy was plus 22.1% before term with a later drop of to plus 3.1%. The average rate of nine women believed to be of the hyperthyroid type was plus 32.2 % before with a drop eleven days post partum, to plus 8.9%. Patients with toxemia of pregnancy had low metabolic readings. Three with edema and little or no albumin had lower readings than a single patient with high blood pressure, albumin, casts, but no edema. The average blood calcium for the patients with thyroid hypertrophy was slightly higher than the average for the women with normal thyroids, but a small series of cases does not warrant conclusions. Three patients with toxemia showed a lowering of the calcium post-partum, while the normal patients usually showed an apparent increase within eleven days. The use of cod liver oil and ultraviolet irradiation did not appear to increase the blood calcium in the few cases studied.

Davis(5) believes, like Yoakam(40), and Falls (9) that metabolic rates well above normal limits indicate abnormal thyroid function, usually of slight degree. The return to normal limits within eleven days post partum, while the rate does not prove that the increased rate did not signify an abnormal function. These patients should be kept under medical observation for a long time after delivery. Many of the so-called neurotics of the past probably had disturbed thyroid function.

Other workers have studied the effect of the basal metabolic rate on pregnancy, but have limited their work to the hypofunction of the gland. One of the foremost of these

is Litzenberg (24). He took his material from 2500 consecutive determinations of basal metabolism in all types of patients, of whom 758 had a rate of minus 10 % or lower. These were divided into two groups, the first of 137 women included all with a low basal metabolic rate, whose records contained sufficiently accurate data to warrant analysis. The second was a group of 52 sterile women, all with low basal metabolism and all treated with thyroid substances. None of the women in either group showed any other evidence of myxedema.

In the first group 78 were married of whom 35 women or 45% were sterile. In addition there were 15 cases of relative sterility or women presenting the following abnormalities:

(a) No living children, but one or more still births, miscarriages or abortions (6 cases) (b) One or more children living but also, one or more still births, abortions or miscarriages (9 cases). Sterility, actual or relative occurred ~~than~~, in 56% of this series, more than four times the incidence in the United States according to Lotha, who says the percentage is 13%. In addition 44% of the 137 women had menstrual difficulties with no pelvic conditions to account for the symptoms.

In the group of 52 women, 33 or 63% had abnormal menses and 28.8% had had abortions. All were treated with thyroid and 17 or 30% of conceptions followed, one becoming pregnant four times and another twice. One had twins and two aborted once, giving a result of the treatment of 16 babies, certainly justifying the treatment. Basal metabolic rates should be taken in all cases of sterility, both in the husband and wife as lowered metabolism, even to a moderate degree, interferes with the reproduction function of a large percentage of cases.

Restoration of the basal metabolic rate to normal will correct a large number of these cases (24).

Brown (1) states that hypofunction of the thyroid, unless producing symptoms of myxedema, probably escapes recognition more frequently than any other condition for which there is specific treatment. The condition appears most frequently between the ages of thirty and forty and is more common in women in a ratio of six to one. Brown's paper is concerned with women who are going through pregnancy.

The symptoms are many and varied. Among the most important are a gain in weight of fifteen to fifty pounds over a period of a few years without any change in habits of eating and exercise, irregularity of menses both in appearance and amount of flow, with amenorrhea the most frequent finding, changes in skin,--a dry

scaly, itching skin with thinness or absence of axillary or pubic hair; seborrheic dermatitis, loss of lustre, brittleness and thinning of hair; frequent attacks of respiratory infection; increased sensitiveness to cold; tendency to be sluggish, especially in the morning; various neuralgic or neurotic pains of shifting nature; obstinate constipation; mental symptoms as melancholia, etc. The patient may complain of only a single one of these symptoms or of many of them and a careful history must be taken.

The condition may be missed as the symptoms and the gain in weight may be assumed as due to the pregnancy and the patient told that she is doing well and will be all right after the delivery. However, this is not the case and she may pass from the hands of the obstetrician to the internist and may not be relieved until someone takes a careful history and basal metabolic

rate. This rate may be minus 10 to minus 50 and the multiplicity and severity of the symptoms has little relation to the metabolic reading. A patient with many signs of myxedema may have a reading of minus 10 or minus 20, and another with very few symptoms may have a reading of minus 30 to minus 40. The significant feature is that the reading is minus and this should call for a thorough study of the case and institution of thyroid therapy.

Brown states further that the metabolic reading during pregnancy in a normal woman should be from plus 15 to plus 25, and any case not showing this physiological increase is, at least, one of potential hypothyroidism.

According to Engelback the normal child at birth should show one ossification nucleus at the upper end of the tibia and two nuclei in the ankle. The absence of these is proof of insufficient prenatal thyroid function.

Witts (39) reported a case of hypothyroidism in a mother and daughter with association of cretinism, diabetes and pregnancy in the daughter. The daughter came in at the age of 21 years complaining of menorrhagea. Her periods started at the age of 19 years and occurred every three weeks, lasting from 1 to 3 weeks. There was no diabetes in the family. The patient was small and childlike, measuring 4 feet 6½ inches, with a dull expression but apparently fairly intelligent. The features were myxedematous, nose broad, ears large, lips thick, hair short, dry and brittle, and hands spadelike. There was no pubic or axillary hair but the uterus and breasts were normal.

The patient was put on thyroid treatment and in less than two years she was back with polyurea, thirst, and weakness, and

a high urinary and blood sugar. Her thyroid treatment was reduced and with a dietary change the sugar disappeared. Later she returned to the hospital and was put on insulin and still later she came in sugar free but with a history of having had no period for three months, and it was found that she was pregnant. Four months after this she was admitted to the hospital in coma, having had no insulin for six weeks. Labor commenced the next day and she was delivered of a 7-8 months fetus showing early maceration. Her breasts secreted milk but she showed a marked anemia.

This case shows that hypothyroidism is inherited and that the condition is a great but not an absolute bar to pregnancy. One would expect that the association of hypothyroidism and diabetes would be rare as sugar tolerance is increased in hypothyroidism. Post mortem findings on cretins and myxedematous persons show an increase in islet tissue in the pancreas in these people. There are only five cases reported of diabetes in juvenile myxedema or cretins and two of these cases were brothers.

Why should we be concerned about hypothyroidism in pregnancy aside from the sterility standpoint? Doan (35) had covered the subject very thoroughly. He states that no child with an abnormal thyroid function can progress normally along the lines of differential development. The thyroid is the pacemaker, the regulator of physical and mental differential development and the leader of the endocrine system. The great prevalence of thyroid insufficiency and the resulting effect on health and character is not realized. Their insufficiency ranges through all degrees, from absence, with utter idiocy,

to extremely mild forms where the deviations from normal are not so marked.

The cretin is an idiot and a dwarf and will always remain an infant in mentality. Attention has been called to the influence of thyroid deficiency in the mother upon the differential development in the later life of the child. Gross development refers to increase in size. Differential development includes all the changes, physical and mental, that occur in the process of evolution from the time of conception until the individual reaches full maturity. Normal differential development is a continuous process by which physical, intellectual, mental, and moral perfection is attained. Later stages follow early stages and the normal baby born with normal differential development is well on the road to healthful maturity and has a better chance than the baby who is retarded at birth.

The thyroid function must be effective early in the life cycle if normal development is to be reached. Adequate function is of more importance during fetal life than at any later stage of development. The child born with retarded development may, if provided with adequate thyroid function at a early age, apparently reach normal, but will never quite reach his inherent possibilities. The result of thyroid deficiency in the mother may not be obvious until the child reaches adolescence, too late to speed up differential development.

The cretin is not the index of economic loss in the community but he is a torch bearer of the incompetents, the absolute zero of intelligence. Outnumbering him many times is the army of cretinoids--weak minded and imbeciles, sluggards

and misfits, deformed, deaf-mutes and degenerates, criminals unfortunate representatives of every phase of decadence from the zero of cretinism to degrees of mentality and physique barely below the normal. It is impossible to estimate the prevalence of the milder forms of physical and mental underdevelopment due to lack of thyroid function. Many attain almost normal physical and intellectual power but are lacking in moral and character qualities.

Is retarded or differential development in these cases due to conditions within our control? The retarded development in many cases can be shown to be the result of thyroid insufficiency in early life. The large group of defectives and morons, those who show slight deviation from the normal, who are slow to learn, finding themselves at the foot of the class, who are given to truancy, who seem normal but are not, who promise but do not keep their promises, who try to but do not succeed, cannot hold their jobs, are burdens and source of constant anxiety to their parents, are prone to yield to criminal impulses, these constitute the greatest social and civic problem that confronts us today.

Can the medical profession, in the light of present knowledge, by preventive measures, especially during pregnancy reduce the incidence of the misfits? Can they, by prevention of thyroid deficiencies in pregnant mothers and growing children enable the coming generation to more nearly approach perfect differential development? The results of appropriate treatment directed toward speeding up the differential development in children attending special schools for the backward children are encouraging. There is hardly a medical practitioner who

does not see several backward children each year. About 95% of all these children are appreciably improved by thyroid medication; but in no such case can one hope to obtain the results possible by earlier attention to the deficiency.

Sloan (35) states that pregnancy is a factor influencing the rate of metabolism just as fever, digestion, exercise, etc., and must be considered as such. Higher ratios of oxygen consumption must be taken and more consideration paid to the emotional state. While most authorities agree on the higher rate, (29) the rate for the different months has not been even approximately standardized.

Many cases of hypothyroidism have been overlooked because the rate was reported normal, no attention having been paid to the fact that the normal reading through pregnancy is probably 20 to 30 points higher than in the same woman if not pregnant. For example, a plus 10 might have been a minus 15 before pregnancy. There are great variations in the basal metabolic rate, especially in the first few months of pregnancy but not in the later months, except at times and for only a few days. If the basal metabolic rate is to be taken as a criterion or guide for treatment, new tables with higher percentages should be adopted as well as further investigations made of the probable factors which cause such great variations in the basal metabolism in pregnancy.

Yoakam (40) believes, with others, that pregnancy calls for increased demands on thyroid function, and, when the diet is deficient in iodine, it leads to hyperplasia of the gland, hyperthyroidism, and congenital goiter in the new born (120 or 34.9% where 64 % of the mothers had prophylactic iodine and this showed up in the first two weeks of life. Where

the mothers had no prophylactic iodine, the incidence of congenital goiter was 60%. Where iodine was given, the incidence was 3.9%.)

The incidence of goiter in 60% of the mothers in his series compared favorably with the results of surveys made upon the general population of Michigan (Goiter belt--1928), and the same incidence in infants of mothers not receiving iodine therapy or prophylactic treatment also corresponds closely to the general incidence and suggests that endemic goiter may have its origin in intrauterine life. Measurement of the neck as a means of determining thyroid enlargement was less accurate than palpation of the isthmus and estimation of the thickness in centimeters.

In trying to answer the question "What effect has hyperthyroidism on pregnancy?" Clate and Daniels (2) have gone over the clinical records of the Lahey Clinic from 1914 to 1929 and selected all patients having both conditions. They found thirteen cases of exophthalmic goiter and two cases of secondary hyperthyroidism complicating pregnancy. In this time interval there were 3678 toxic patients operated upon. Of this group 887 were adenomatous goiter with secondary hyperthyroidism and 2791 had primary hyperthyroidism. The incidence of pregnancy in their experience was .41%. It is common knowledge that the incidence of hyperthyroidism in pregnancy is very low, and there were no cases of hyperthyroidism in 937 obstetrical patients studied by Yoakam (40). At the Mayo Clinic only 42 cases of pregnancy were found in 7228 cases of hyperthyroidism. The fact that diminutions of menstrual function often accompaniesth thyroid toxicity, and that the

more severe the hyperthyroidism, the less active the ovarian function, may well be related in some degree to the lack of fertility in thyrotoxic women. These workers put the metabolic rate in these women at a point of at least plus 30 and other clinical symptoms must be pronounced to make the diagnosis. They have also stated that hyperthyroidism may be confused with nervousness of pregnancy in some women, but this has been taken up before.

Opinions vary on the effect of hyperthyroidism on the course of pregnancy. Gardner-Hill (12) found from numerous statistics that the results of pregnancy in exophthalmic goiter were very poor and 50% of these cases ended in miscarriages or premature birth. On the other hand statistics from the Mayo Clinic (34) showed definitely that the complication of hyperthyroidism caused no more miscarriages than resulted in normal women. The experience of Clute and Daniels (2) agrees with the latter. Their records showed 18 patients with definite hyperthyroidism while pregnant and 16 of these had exophthalmic goiter while 2 had adenomatous goiter. Three of the 18 had thyroidectomy after delivery and subtotal thyroidectomy was carried out in the remaining 15 cases during their pregnancy and all recovered. One miscarried after a long ride home from the hospital; eight days after operation. The three not operated until after delivery had normal children and did well after deliveries, thus it is concluded that hyperthyroidism does not cause disastrous termination of the pregnancy in the majority of cases.

The question of the effect of pregnancy on hyperthyroidism is not so easily answered. There are so many factors influencing

the individual case that it is hard to establish one as more significant than another in analyzing the end result. Also, frequent metabolism studies must be made, allowing for the normal rise of pregnancy. H. Gardiner-Hill (12) and Hyman and Kessel (21) believe that there is no evidence that pregnancy makes thyrotoxic cases worse, but, on the contrary, that many cases improve during pregnancy and maintain this improvement afterwards. L. Seitz believed that pregnancy did not affect the hyperthyroidism in 40 percent of his cases, but in 60% the condition was made much worse. Mussey, Plummer and Boothby (26) did not find that pregnancy made the course of the hyperthyroidism any more difficult to handle or influence it to any degree. Clute and Daniels (2) did not see anything occur in hyperthyroids with pregnancy that did not commonly occur in the non-pregnant thyroid cases of similar type. They believe, however, that pregnancy during hyperthyroidism is an added load for the patient whether or not it effects the hyperthyroidism that is present. Pregnancy must increase the patients muscular work and add to the metabolic requirements. It was their daily experience that thyrotoxic patients could not tolerate additional loads, and they feel that pregnancy is a serious burden in thyroid intoxications.

Another problem to be solved is the effect of the disease on the baby. In the above series the cases who went to term had living babies, all of them normal. There were no congenital defects, no goiters and no evidence of insufficient thyroid function. There was no evidence whatever that a baby born of a thyrotoxic mother would be abnormal in any way.

The possibility that pregnancy is related to the occurrence of hyperthyroidism has frequently been suggested. The fact that

pregnancy is so commonly accompanied by some thyroid enlargement has doubtless given strength to this suggestion. Any proof of this theory is difficult and studies, unless striking, are apt to be misleading. A series of 102 consecutive cases of hyperthyroidism have been studied in the attempt to learn something of the relationships between the occurrence of the pregnancy and the onset of the hyperthyroidism. Many of these cases had to be excluded, so only 203 could be investigated. Of these 203 replied, who were women of childbearing age.

In this group 41 stated that the onset of their hyperthyroidism was dated within three months of delivery. That is, 12% of the women in the large group of 347 had been pregnant within three months of the onset of their hyperthyroidism. This is not such a striking relationship that it will permit any deductions that pregnancy was or was not a factor in the hyperthyroidism.

The figures tended to prove that there were, if anything, fewer pregnancies before the onset of hyperthyroidism in this group. Of 118 of the 203 were married and under 40 years of age, 90 had had at least one pregnancy before the onset of hyperthyroidism. If it be admitted that 10% of all marriages are childless it is seen that 90 pregnancies in 118 women is definitely below the normal expectation. This tends to prove that pregnancy is not an etiologic factor in hyperthyroidism. This further is borne out by the study of pregnancy occurring after thyroidectomy for exophthalmic goiter as 53 of the 203 women bore 69 children after thyroidectomy and in only one case was there even a question or recurrence of thyrotoxic symptoms during the pregnancy, and the puerperium. This case was controlled with Lugol's solution and may or may not have been a recurrence. At any rate, the

the fact that 69 pregnancies failed to produce any serious return of hyperthyroidism in any one of 53 patients, is, in the opinion of the author's very good evidence that pregnancy is not a very potent factor in the etiology of hyperthyroidism.

The fetal mortality rate in this group was 20% and this figure is certainly within the normal expectation of abortion or miscarriage among a group of normal women.

One cannot help but be impressed with the rarity of the association of hyperthyroidism and pregnancy as pointed out by Mussey, Plummer and Boothby (26) who found in the records at the Mayo Clinic that of a group of 5043 women with exophthalmic goiter only 32 were pregnant and of 2185 women with adenomatous goiter only 10 were pregnant. Thus, of the entire group of 7228 women only .6% were pregnant. This confirms Markie's statement made in 1918 that approximately 100,000 women at the New York Lying In Hospital, only 8 appeared to be suffering from hyperthyroidism. In the cases of this series there was no evidence that pregnancy influenced the course of exophthalmic goiter. Some stated that their symptoms were better and there were others that were aggravated by pregnancy. This is of little significance as the course of the disease varies but it would be thought that the double load would not be stood so well. In only two out of the 32 cases of exophthalmic goiter could the onset of the disease be considered, with reasonable certainty to have developed during pregnancy. In each of these the onset was rapid and severe and the symptoms characteristic of the crisis stage of the disease, but in both it was mistaken for vomiting of pregnancy.

Thirty women became pregnant during the course of the goiter, mostly during a period of remission of the disease; three of these after ligation of the superior thyroid arteries and three during recurrences of the disease after partial thyroidectomy. Of these women, 23 delivered at term, two aborted and two delivered prematurely, two were not delivered and three could not be traced. One of the abortions was at 6 weeks after the patient had returned home for rest and observation prior to partial thyroidectomy. The other at three months 17 days after a second ligation of the superior thyroid artery.

All of the 10 patients having adenomatous goiter became pregnant after the onset of hyperthyroidism. None of the mothers died and nine were delivered of normal babies; one baby still-born due to dystocia. All but one of the mothers had had some form of operative treatment on the thyroid gland.

In all of these cases serious additional complications were not more frequent than is usual in either condition alone and therapeutic abortion was not necessary. The course of pregnancy and the maternal and fetal mortality were not appreciably affected as the result of the syndrome due to exophthalmic goiter or adenomatous goiter with hyperthyroidism, nor, on the other hand did the pregnancy render the control of these two conditions noticeably more difficult.

The studies of H. Gardiner-Hill showed that the presence of persistent, simple, adolescent goiter did not appear to affect the normal incidence of pregnancy. The expectancy of pregnancy in this group was also up to normal, although there were several instances of miscarriages following repeated pregnancies in patients with untreated thyroid or with definite signs of

of hyperthyroidism. The effect of pregnancy on the goiter in these primarily adolescent cases was in almost every instance the same, i.e., a further hypertrophy of the gland. In spite of this, most of these patients developed well marked signs of hypothyroidism in later life. The incidence of pregnancy in the group who developed a simple goiter in adult life was below average expectancy: only about 50% became pregnant at all. No harmful effect was noted on the pregnancy although it was usually associated with hypertrophy of the gland and later symptoms of hypothyroidism.

Pregnancy as an event complicating preimary Grave's disease occurred in about half the cases in which it was possible, but more than one pregnancy after the onset of the disease was comparatively rare. The results of pregnancy in those cases were poor, for there was an unsuccessful termination of pregnancy by miscarriage or premature birth in 50%. During pregnancy there is almost invariably an amelioration of the symptoms. In about 50% this improvement was maintained afterwards.

The incidence of pregnancy in secondary Grave's disease was low, only two instances out of nine possible cases. The results and the effect on the subsequent course of the disease were unsatisfactory, but the number of cases was too few for definite conclusions. The practical bearing of the facts was: a patient with simple goiter, whether developing in adolescence or adult life, may be safely advised to entertain the prospect of pregnancy. The thyroid condition should be treated before and after the event. If this is not done the thyroid will enlarge and later symptoms of hyperthyroidism will develop.

Pregnancy in Grave's disease is a different story. (see results of Mussey, Plummer and Boothby).

In the series studied, the miscarriages(9), prematures (1), and still births (2) out of 23 patients, may have been the result of shocks, mental stress and inadequate rest and treatment, for the results were generally good if the conditions were generally satisfactory. Every precaution must be taken and it must be remembered that the symptoms are usually ameliorated, as was also found by Kyman and Kissel (21). A prospect of pregnancy may be entertained by a patient with previous Graves disease if the circumstances are favorable and previous treatment adequate, the degree of intoxication not too great, and cardiac and other complications absent. Under such circumstances there not only seems to be a good chance for the pregnancy to be carried to term, but in these cases there is an equally good chance of the disease being permanently benefited. The outlook in cases of secondary Grave's disease does not appear to be so satisfactory. (12)

Thus far, the treatment of hypothyroidism and hyperthyroidism in pregnancy has been merely mentioned from time to time, but little definite information has been given. It is impossible to close without some consideration of treatment because of the importance of this phase of the subject.

Hypothyroidism will be considered first and Brown has stated that patients known to exhibit hypothyroidism before conception should have frequent checks of metabolic rate and thyroid extract in increasing dosage sufficient to maintain a plus reading if possible. This is true preventive medicine and assures the development of a normal child without marks of cretinism. Should sufficient thyroid not be given, the child will show definite defects in bony structures, in that certain nuclei

normally present, are very small or even absent. This has been mentioned previously. The absence of these nuclei are proof of insufficient prenatal thyroid dosage and the child should be given thyroid extract in doses of 1 grain daily at 2 weeks of age, increasing $1\frac{1}{8}$ grain each month until the proper dosage of between 1 and 2 grains is reached, this being determined by the elevation of the rectal temperature to 100 degrees. If the mother is nursing the child, some benefit may be had by giving her thyroid extract but usually this is not sufficient.

In hypothyroid patients the tendency is not to give large doses of the extract, however, enough should be given to raise the basal metabolic rate to plus 15 and keep it there. It may take one grain per day or it may take 30 grains. The amount to be taken may vary from month to month and the patient can usually tell early when the hypothyroid symptoms are returning, due to the sluggish feeling and gastro-intestinal symptoms. The change in dosage may have to be extremely marked as in one case cited, where the dosage jumped from 3 grains a day early in pregnancy to 22 grains in the last two months. Exercise was taken every day with little fatigue and the pulse was kept between 54 and 95, and the attempt was made to keep the basal metabolic rate up to plus 16 %/ There was no restriction of diet and there was a feeling of well being throughout the entire pregnancy with no nausea or vomiting. Delivery was spontaneous and without abnormal events. The child was normal in every way and thyroid was given for 15 days when the child was 7 months old because of loss of appetite and failure to gain. At 1 year the child had normal bony development. Thus the treatment may be tedious

but can be accurately controlled by frequent basal metabolism readings, and Brown(1) found that as much as 8,880 grains of thyroid extract can be given in 1 year without symptoms of overdosage.

Witts (39) treated a mother and daughter with thyroid extract, gr. $\frac{111}{3}$ (3) per day and they showed steady and remarkable improvement. The daughter, who was 21 years of age, gained 1 inch in height in 2 years and her symptoms disappeared entirely.

The work of Gardiner^o Hill, Butt and Smith (36) indicates that thyroid treatment does not have a harmful influence on the sugar tolerance of the adult myxedema. Others find that a temporary glycosurea may result from thyroid administration to others, but myxedematous types. Danger of producing glycosurea in thyroid administration is not to be feared.

Sloan (35) has stated that treatment of hypothyroidism consists largely in the administration of thyroid and in the correction of mineral deficiencies. Valuable adjuvants are photo-therapy, change of climate, hygienic measures, etc. In the administration of thyroid, large doses are rarely necessary. The amount required daily may usually be given in one dose, as $\frac{1}{2}$ to 1 grain of thyroid extract per day is usually sufficient. The correction of mineral deficiencies requires more thought and study. Iodine, the most important mineral is easily assimilated in almost any form usually Lugol's sol., 5--10 drops twice a day. There are several preparations for the other minerals and light therapy should be given in association.

As to the treatment of hyperthyroidism there has been some discussion pro and con in the past few years. Formerly, interruption of pregnancy was usually advised in severe cases (Gellhorn)

It has since been demonstrated that the operation of partial thyroidectomy in cases of adenomatous goiter with hyperthyroidism and since 1922, the use of compound solution of iodine internally in cases of exophthalmic goiter, followed by partial thyroidectomy, when this procedure is indicated, enable the pregnant woman to carry through with reasonable expectancy of health and normal living offspring. (27)

Plass and Yoakam have pointed out that prophylactic iodine during pregnancy is of little value in preventing gestational hypertrophy of the thyroid, providing the gland is of normal size originally, but is useful in preventing such hypertrophy in colloid goiter and may even lead to a decrease in size. Davis (5) found iodine to be beneficial in the normal case. In only one case was there evidence that iodine may have done any possible harm. The protective effect on the fetal thyroid of iodine administered to mother during gestation adds considerable to the argument for such prophylaxis. Without this approximately $\frac{1}{2}$ of all the babies born in a region of endemic goiter will show some thyroid enlargement, but that that under any form of iodine administration the evidence is considerably diminished, with iodine salt being apparently particularly effective.

Hinton (20) has said that there are two types of hyperthyroidism, (1) adenomatous or nodular goiter, (2) exophthalmic goiter or Grave's disease. The fundamental differences in the two types of hypersecretion must be understood. Some clinics believe that these are separate conditions, and that the management of one should be different from that of the other, but this distinction does not seem to be warranted at present. Plummer (30) believes that Lugol's solution is of value in

exophthalmic type but is contraindicated in the adenomatous type as preoperative medication. Graham (15) proved that iodine was beneficial to both types, but that smaller doses could be given in the adenomatous type. A clinical diagnosis of adenomatous goiter is not infrequently made and the pathological report may come back with histologic diagnosis of Grave's disease. The same holds true in typical cases of exophthalmic goiter that have received iodine therapy. Hinton (20) has cited cases which prove the above to be a fact.

It is essential to look upon hyperthyroidism during pregnancy as one continuous process and not as separate diseases. It is difficult to be certain of a diagnosis unless the clinical picture and the histologic sections are studied together, but for the clinical management it is essential to divide the patients into acute and chronic stages of hyperthyroidism, as exophthalmic goiter and adenomatous goiter. Chronic hyperthyroidism or hyperthyroidism from a nodular or adenomatous goiter usually occurs in women who have born several children in rapid succession and who say an enlargement of the thyroid was noticed after the birth of the first or second child, while the symptoms of hyperthyroidism may not develop until after the third or fourth pregnancy. The treatment here depends on the patient's condition and her desire to have more children. If the case is fairly mild with a basal metabolic rate not exceeding plus 30, the patient can probably be carried through a normal pregnancy without any undue risk of permanent cardiac change. But, if at the beginning of pregnancy there is a high basal metabolic rate with definite cardiac involvement, termination of pregnancy is advisable, and if the patient does not wish to submit to that, the only alternative is thyroidectomy.

after proper preoperative treatment.

Exophthalmic goiter usually develops in the first months of pregnancy, more frequently in primiparae. The treatment depends entirely on the condition of the patient when first seen. Unless she is critically ill it is not necessary to interrupt the pregnancy but a thyroidectomy can be performed and the patient carried through a normal delivery. If the case is mild it may be possible to carry the patient through her pregnancy on medical management and defer the more radical measures until later. Hinton (20) believes that it is safe to estimate that 90% of cases of hyperthyroidism associated with pregnancy can be carried to a normal delivery if properly managed. He also believes that colloid goiter is the one type most frequently encountered and that this is not only curable by treatment with thyroid extract or iodine, but that this also prevents adenomata in later life, and thus reduces the incidence of thyroid malignancy. (19)

Falls (9) has approached the subject from two different points of view, namely, from that of the surgeon and from that of the obstetrician. The surgeon rather disregards the pregnancy and is concerned only with the goiter. On the other hand, the obstetrician is of major importance to the obstetrician and the goiter and its symptoms are only one phase of the major problem. In a given case of thyrotoxicosis the surgeon may advise medical treatment until the symptoms abate and then recommend partial thyroidectomy or ligature of the poles to decrease the symptoms. If the patient aborts following this treatment it is a regrettable incident but the wisest course to pursue. He may feel, that even under medical treatment, there may be a toxicosis as a result, which in itself

will produce abortion and may result in the death of the mother whether or not she is operated.

The medical man and the obstetrician are apt to follow a different course. The patient may be put to bed and given Lugol's solution. The basal metabolic rate is carefully determined and progress watched under this régime. If improvement is continuous they advise against operation, at least until viability of the child, at which time the baby is relatively safe even though the mother's condition is jeopardized by the increased strain of labor. This may be advised even if the operation has eventually to be resorted to.

Davis (5) has advocated iodine during pregnancy as a prophylactic measure in goiter belts, unless adenoma is present. Iodine hyperthyroidism is recognized as a possibility but thus far has not been observed. Patients previously operated on for toxic goiter are usually benefitted by taking small doses of iodine during pregnancy but some apparently can not tolerate the drug. He has reported one case successfully operated in the fourth month of pregnancy and later placed on iodine medication. Another patient with history of a toxic adenoma took iodine during pregnancy with apparent benefit, although she had a basal metabolic rate of plus 86 at term. She was successfully operated 20 days post mortem. Prolonged nausea and vomiting, which was evidently due to a crisis of exophthalmic goiter, in a patient with a basal metabolic rate of plus 81, was successfully treated with iodine therapy.

Pregnant women with symptoms of exophthalmic goiter and with basal metabolic rates as high as plus 110 have been treated by rest, Lugol's solution and occasional mild

sedatives over a period of months without serious aggravation of symptoms. They have been allowed to go into labor and to deliver spontaneously or with forceps assistance. The fetal mortality is no higher in these cases than in the normal. The reason for the divergence of opinion between the surgeon and the obstetrician may be explained by the fact that the pregnant woman, because of associated changes in the ductless glands, may react differently to the clinical syndrome called thyrotoxicosis. She may be able to adjust herself without operative interference. These patients should be treated more conservatively than the same woman who is not pregnant. Another reason for conservatism is that after parturition the symptoms may spontaneously disappear and operation can be indefinitely postponed or only undertaken if the symptoms persist. It is conceivable that operation during the artificial hyperthyroidism of pregnancy, of it may be called that, may result in hypothyroidism after the pregnancy. Therapeutic abortion should be done only after both medical and surgical intervention have failed.

Cases have been reported (10) of patients in which the thyroid has been removed for exophthalmic goiter and the patients have later become pregnant. They are capable of going through pregnancy in a perfectly normal manner but the prenatal care must be closely supervised. Lugol's may be given if toxic symptoms supervene and advise against all unnecessary work and worry must be given. The question frequently comes up as to whether or not a woman with evidence of thyrotoxicosis especially of the exophthalmic type, should be operated on during the pregnancy. The answer of the surgeon and especially

those of the most experience in goiter surgery as the Mayo clinic, LeHay Clinic, Nelson Percy and Seed is an emphatic yes. (10)

Williamson (38) believes that no thyroid patient after operation should become pregnant for at least two years, even though the symptoms are alleviated. If she does, she must be treated cautiously with iodine, thyroid substance, sedatives and rest and basal metabolic readings must be taken for the accurate estimate of the case. Even then the patient cannot be assured that she will have a normal baby, if she is still having symptoms of such a nature that they may be referred to the thyroid.

Smith feels that, following delivery, if the patient with toxic goiter has pelvic symptoms also, that the goiter must be taken care of first. (36)

After a two year study of dogs and humans, Graham (15) found that when a thyroid is hyperplastic and hypertrophic that iodine was indicated but that it had no value in a colloid ~~or~~ resting goiter. He was unable to recognize a single symptom or sign that was necessarily pathognomonic for exophthalmic goiter as opposed to toxic adenoma. Neither were anatomic or histologic alterations pathognomonic for either one. There are equally good reasons for speaking of dysthyroidism in case of toxic adenoma and exophthalmic goiter and equally good reasons for speaking of hyperthyroidism in both. The degree of hypertrophy and hyperplasia of the gland determines the quantity of iodine that will be tolerated, and the reaction to iodine is fundamentally the same in both conditions; thus there is no alternative but to regard them as clinical variations

of a single morbid state.

Fahrni has found that where pregnancy and hyperthyroidism both exist in a woman less than five months pregnant, thyroidectomy is the preferable procedure to follow. The risk to the patient is not greatly increased with pregnancy and the danger of miscarriage is slight. He met with no miscarriages or abortions under this treatment. After operation the patient is able to go through a normal delivery and remain in good physical condition. The interruption of pregnancy at three to five months is more dangerous than thyroidectomy. In women six to nine months pregnant, conservative treatment is the method of choice and operation may be carried out some time after delivery. He also believes that women should be advised against pregnancy for at least two years after operation but if they do become pregnant there is no reason to terminate the pregnancy.

CASE HISTORIES

(From personal observation)

CASE I: Mrs. V. M. a white housewife, age 32 years, was admitted to the University Dispensary complaining of a tumor of pregnancy. She gave a history of nervousness since she was 17 years of age and this became more noticeable with each pregnancy. With her last pregnancy, eight years before she had had some edema. There was slight edema with the present pregnancy which was connected with low protein diet and $MgSO_4$. When seen, she was almost four weeks overdue and two medical inductions had failed. She showed marked tremor, had palpitation, pulse of 100 to 110, and there was a palpable adenomatous mass in the left lobe of the thyroid. She admitted three or four induced abortions. The patient was sent to the University Hospital for a bag induction. No basal metabolic rate had been taken. She had normal delivery $4\frac{1}{2}$ weeks after the estimated date of delivery. Recovery of mother and child were uneventful.

CASE II. Mrs. V. Age 29, black housewife, delivered in December at the University Hospital. She had normal delivery but after one month after leaving the hospital she noticed some difficulty in swallowing. She reported to the dispensary in February and her only complaint was an enlargement

in the left aspect of the neck, with a feeling of tightness in the throat. Diagnosis was made of carcinoma of the thyroid gland or a possible thyroiditis. She has not yet been admitted to the hospital for operation.

CASE 111. Mrs. L. A white, housewife, age 36 years was seen in the Home last fall. She showed marked symptoms of exophthalmic goiter with tremor, palpitation, nervousness, large swelling of the thyroid gland and exophthalmos. She had had no symptoms until her second pregnancy, at which time she noticed the swelling in the neck and nervousness. She had five children varying in age from 6 to 14 years. She stated that her condition had become worse with each succeeding pregnancy but that there seemed to be an amelioration of the symptoms between pregnancies. In the past 4 years, however, the condition has become increasingly more marked and she was told to report to the dispensary for treatment and studies of the basal metabolic rate. Thus far she has not reported.

CONCLUSIONS

1. Both hypothyroidism and hyperthyroidism may be overlooked in pregnant women and the symptoms attributed to the pregnancy.
2. Both of these conditions are fairly common even though women suffering from thyrotoxicosis and improper function of the thyroid do not conceive easily.
3. The diagnosis is best made by a series of careful basal metabolism readings, allowance being made for the normal physiological rise in the pregnant state.
4. In cases of sterility careful studies should be made of the basal metabolic rate to rule out hypothyroidism.
5. The best treatment of hypothyroidism in pregnancy is prophylactic, and iodine salt should be given, in varying dosages, to pregnant women, depending on the severity of the condition.
6. Prophylactic use of iodine will decrease the incidence of congenital goiter and hypothyroidism in the new-born.
7. Conservative treatment, including bed rest, Lugol's solution and frequent basal metabolism tests should be tried first in treatment of thyrotoxicosis.
8. Most of the cases of exophthalmic goiter and adenomatous goiter will do well on conservative treatment and can usually be carried through pregnancy without serious complication.
9. Patients should not be operated upon until some time after delivery, unless conservative medical treatment fails.
10. If operation is necessary during the pregnancy, it is fairly safe in the first five months of the pregnancy, and

the percentage of miscarriages and abortion is no greater than in the normal pregnancy.

11. Careful medical treatment and frequent metabolism tests are necessary following the operation, to assure good physical condition of both mother and child.
12. A woman should not become pregnant for at least two years after operation, but if she does she can usually be carried through a normal delivery.
13. Children showing evidence of thyroid deficiency may be treated early with dosages of thyroid extract up to 2 grains per day.
14. It is quite possible that hypothyroidism can be prevented in children if proper treatment is given the mother during her pregnancy.
15. All women with severe upsets during pregnancy should have careful metabolic tests at frequent intervals to rule out thyroid disease.

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